Pharmacological Basis of Therapeutics" teaches treating bone-resorption disease, osteoporosis, comprising administering various medications, including anti-resorptive agents such as calcium, estrogen, calcitonin, bisphosphonates. The Examiner admits that the primary references does not teach a kit comprising the elected species of iNOS inhibitor, L-N-6-(1-iminoethyl)lysine, nor does it teach a method for treating osteoporosis using the same. Hukkanen et al. are said to disclose that cytokines such as IL-1β induce other cytokines such as IL-6, which have already been shown to increase bone resorption. This can be inhibited by inhibitors of NOS activity. Moore et al. are said to disclose that L-N-6-(1-iminoethyl)lysine is a potent and selective inhibitor of iNOS.

This rejection is respectfully traversed. The primary reference, hereinafter referred to as "Reference 1", teaches that estrogen is an antiresorptive agent and can conserve bone mass. That is, estrogen is an antiresorptive agent as well as a bone mass-maintenance drug. However, it is not always true that an antiresorptive agent acts as a bone mass-maintenance drug. Even if it is true that a bone mass-maintenance drug inhibits bone resorption acts as a bone-maintenance drug. In fact, while many compounds have an inhibitory activity of bone resorption, they rarely exhibit a bone mass-

maintaining activity. An antiresorptive agent which also acts as a bone mass-maintenance drug cannot be easily found until the bone mass-maintaining activity is examined.

In Reference 1, it is described that estrogen conserves bone mass and interferes with recruitment of osteoclast precursors (*i.e.*, exerts antiresorptive activity) by decreasing IL-6 production in osteoblasts. (It should be noted that Girasole et al., 1992, "17 β-estradiol inhibits interleukin-6-production by bone marrow-derived stromal cells and osteoblasts *in vitro*: a potential mechanism for the antiosteoporotic effect of estrogens," cited in Reference 1, only described *in vitro* evidence. However, all compounds which decrease IL-6 production cannot exert an antiresorptive activity, and all compounds having an antiresorptive activity cannot act as a bone mass-maintenance drug. Consequently, there is no teaching or suggestion in Reference 1 that a compound which inhibits IL-6 production acts as a bone mass-maintenance drug. Therefore, one skilled in the art would not expect that decreasing IL-6 production would act to maintain bone mass.

Furthermore, as the Examiner is well aware, many factors in addition to IL-6 contribute to bone loss. The relationship between estrogen and IL-6 as described in Reference 1 is not applicable to many cases, for example, to senile osteoporosis. Therefore, it is incorrect to

assume that the relationship between estrogen and IL-6 is a universal explanation for bone turnover.

Hukkanen et al. disclose that induction of IL-6 is completely inhibited by "NOS inhibitors." However, it should be noted that Hukkanen et al. do not teach that induction of IL-6 can be inhibited by a "selective iNOS inhibitor" as used in the present invention.

Moore et al. add nothing to the disclosures of Reference 1 and Hukkanen et al., as Moore et al. merely disclose that the elected species of iNOS inhibitor is a potent and selective inhibitor of iNOS.

Therefore, one of ordinary skill in the art would not have been motivated to arrive at the present invention, namely, a method for treating a bone resorption-associated disease comprising administering to a subject in need thereof an effective amount of a selective iNOS inhibitor from the combination of references cited.

Claims 15-18 are drawn to kits comprising the elected species of iNOS inhibitor, L-N-6-(1-iminoethyl)lysine. However, as noted above, because claims 8-11 are patentable over the art cited, it is believed that claims 15-18 are also patentable over the art cited.

In view of the above, it is respectfully

submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

Respectfully submitted,

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